

## EXTENDED REPORT

# Infectious CNS disease as a differential diagnosis in systemic rheumatic diseases: three case reports and a review of the literature

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**Background:** Immunosuppressive treatment of rheumatic diseases may be associated with several opportunistic infections of the brain. The differentiation between primary central nervous system (CNS) involvement and CNS infection may be difficult, leading to delayed diagnosis.

**Objective:** To differentiate between CNS involvement and CNS infection in systemic rheumatic diseases.

**Methods and results:** Three patients with either longstanding or suspected systemic rheumatic diseases (systemic lupus erythematosus, Wegener's granulomatosis, and cerebral vasculitis) who presented with various neuropsychiatric symptoms are described. All three patients were pretreated with different immunosuppressive drugs (leflunomide, methotrexate, cyclophosphamide) in combination with corticosteroids. Magnetic resonance imaging of the brain was suggestive of infectious disease, which was confirmed by cerebrospinal fluid analysis or stereotactic brain biopsy (progressive multifocal leucoencephalopathy (PML) in two and nocardiosis in one patient).

**Discussion:** More than 20 cases of PML or cerebral nocardiosis in patients receiving corticosteroids and cytotoxic drugs for rheumatic disease have been reported. The clinical aspects of opportunistic CNS infections and the role of brain imaging, cerebrospinal fluid analysis and stereotactic brain biopsy in the differential diagnosis are reviewed.

Central nervous system (CNS) involvement may become a severe complication of several autoimmune disorders. In systemic lupus erythematosus (SLE) between 18 and 67% of patients have CNS involvement.<sup>1–5</sup> Symptoms include psychosis, mood disorders, seizures, acute confusional states, stroke, migraine, chorea, aseptic meningitis, transverse myelopathy, as well as subtle cognitive impairment.<sup>6</sup> There are no specific laboratory or magnetic resonance imaging (MRI) findings, making a proper diagnosis often difficult. MRI may be negative despite overt neuropsychiatric symptoms.<sup>7,8</sup> Cerebrospinal fluid (CSF) analyses may show mild lymphocytic pleocytosis, raised protein levels, and IgG indices as well as oligoclonal bands in 25–50% of cases.<sup>9–10</sup> In up to 81% of the cases CNS lupus may occur without systemic SLE activity,<sup>4</sup> often leading to a delayed diagnosis.

In Wegener's granulomatosis (WG) cerebral involvement is rare (2–8%).<sup>11–13</sup> Forty years ago a review by Drachman described three patterns of CNS involvement in WG<sup>14</sup>: (a) vasculitic changes; (b) meningeal involvement due to adjacent granulomatous disease; and (c) isolated granulomatous meningocerebral lesions. In recent MRI studies Murphy *et al* reported about 30% meningeal thickening and contrast enhancement, 26% meningeal involvement by extracerebral granulomatous disease, 20% cerebral infarcts, and about 50% non-specific white matter lesions.<sup>15</sup> The main clinical manifestations are headache, seizure, or loss of function owing to focal lesion and stroke. Usually the diagnosis of WG is well established before CNS involvement occurs.<sup>16</sup> There are no specific findings in WG suggesting CNS involvement. CSF analysis often shows only a slight rise in protein and a mild lymphocytic pleocytosis. The diagnosis is made by clinical findings, MRI of the CNS, and histology.

Primary angiitis of the CNS is a very rare disorder.<sup>17</sup> The diagnosis is based on the presence of neurological dysfunction, angiographic features of vasculitis (vessel irregularity,

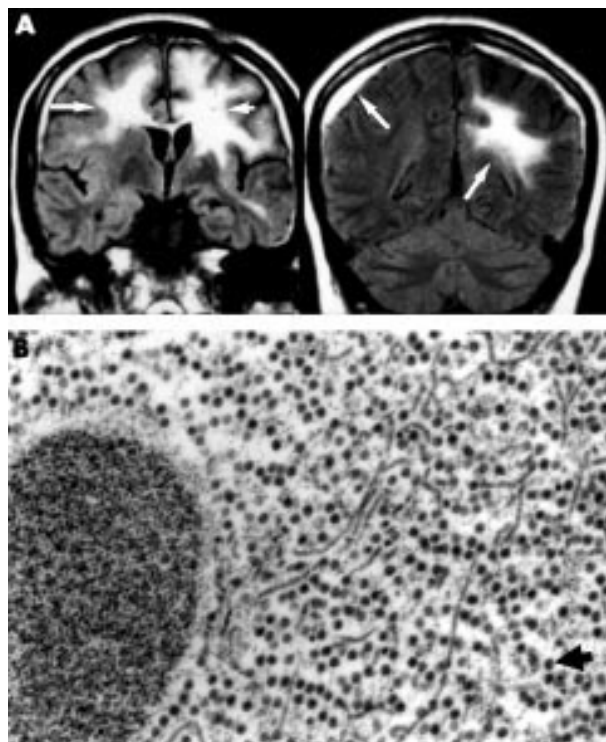
aneurysms, stenosis) and, if possible, stereotactic biopsy.<sup>17–19</sup> MRI findings include infarction and white matter lesions, but both are non-specific.<sup>20–21</sup> The diagnosis of this entity remains problematic and requires the exclusion of more common conditions.<sup>22</sup>

Other autoimmune diseases with common CNS involvement include polyarteritis nodosa, antiphospholipid antibody syndrome, and Behçet's disease.<sup>23–24</sup>

Chronic dysregulation of the immune system in conjunction with immunosuppressive treatment predisposes patients with systemic autoimmune diseases to infections. Therefore the new onset of CNS symptoms always leads to the suspicion of underlying infections in the differential diagnosis of these patients.

Several viruses, bacteria, and fungi can imitate the clinical and the radiological picture of CNS involvement of the primary autoimmune diseases. Therefore careful evaluation of the CNS manifestation is essential because the impact on the therapeutic decision is great. However, the diagnostic procedure is limited by time because in all patients with severe CNS involvement prompt treatment should be instituted in order to preserve the maximum of cerebral function. In this paper we report the cases of three patients with infectious CNS involvement imitating autoimmune disorders. We also review the literature and suggest a standard diagnostic procedure in

**Abbreviations:** ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; CMV, cytomegalovirus; CNS, central nervous system; CRP, C reactive protein; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IV, intravenous; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PML, progressive multifocal leucoencephalopathy; SLE, systemic lupus erythematosus; VZV, varicella zoster virus; WG, Wegener's granulomatosis



**Figure 1** (A) Coronal MRI scan of the brain showing confluent foci (arrows) of hyperintensity in the deep and subcortical white matter and subdural space on inversion recovery sequences (patient 1). (B) Electron micrograph of a brain biopsy specimen (patient 1): Nucleus of a transformed oligodendrocyte with multiple electron dense particles typical for polyoma viruses (arrow). Magnification  $\times 66\,300$ .

patients with pre-existing autoimmune disease and new onset of CNS disease.

## CASE REPORTS

### Patient 1

A 33 year old woman was admitted to our hospital with progressive personality alterations, impairment of concentration and memory, difficulties in word finding, headache, and dysarthria. Eleven years ago SLE was diagnosed by the presence of antinuclear antibodies (titre 1/6000), increased DNA binding, photosensitivity, aphthosis, Jaccoud's arthritis, anaemia, and leucopenia. She had been treated with prednisone doses adjusted to disease activity (7.5–25 mg) and various immunosuppressive drugs: initially, azathioprine; later, chloroquine, danazol, cyclosporin A; and, finally, methotrexate. Five months before admission immunosuppressive treatment was switched from methotrexate to leflunomide (20 mg/day) because of gastrointestinal symptoms and persistent arthralgias.

On admission, laboratory analysis showed a moderate leucocytopenia ( $3.2\text{--}4.2 \times 10^9/\text{l}$ ) with lymphocytopenia ( $0.7\text{--}1.0 \times 10^9/\text{l}$ ). The number of CD4+ T cells was decreased ( $0.24 \times 10^9/\text{l}$ ; normal range  $0.31\text{--}0.53 \times 10^9/\text{l}$ ), resulting in a slightly raised CD4/CD8 ratio (2.81; normal range 1.4–2.4). Antibodies against dsDNA were positive, CH<sub>50</sub> was not decreased, but C3d was slightly raised (10.6 mg/l; normal range <10). T<sub>2</sub> weighted MRI of the brain showed confluent, hyperintense, white matter lesions of the left sided frontotemporal and high parietal region and the right sided supraventricular region (fig 1A). In addition, spotted hyperintense lesions of the left sided thalamus, basal ganglia, capsula interna, and spotted white matter lesions of the right temporal region were visible. The lesions were not enhanced by gadolinium-DTPA and had low signal

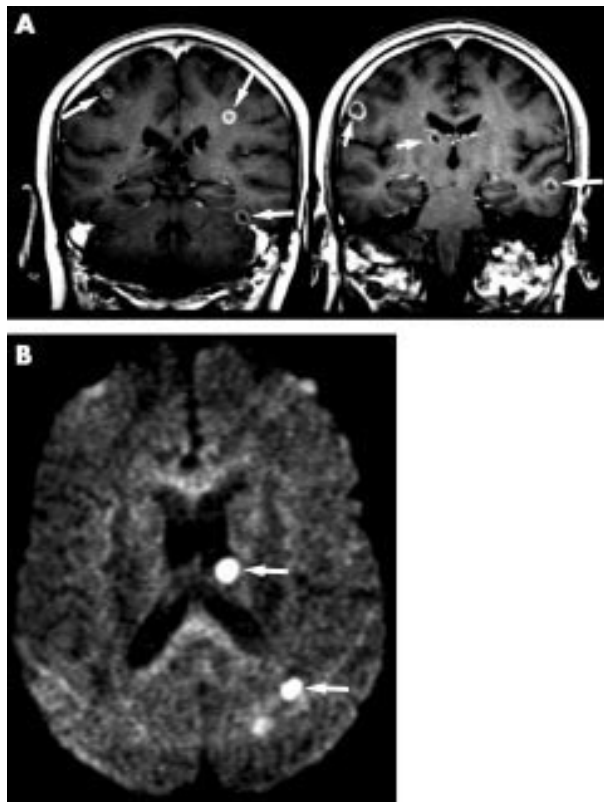
intensity on T<sub>1</sub> weighted imaging. CSF analysis showed a normal cell count, an increased total protein content (652 mg/l), an IgG index of 0.5, and positive oligoclonal bands. A stereotactic brain biopsy was performed that showed abnormal oligodendroglial cells, demyelination, and swollen astrocytes associated with inflammatory cell infiltrates, suggesting the diagnosis of progressive multifocal leucoencephalopathy (PML). The diagnosis was confirmed by electron microscopy (fig 1B) and the detection of JC virus DNA in the brain tissue (nested polymerase chain reaction (PCR)) and in CSF samples (quantitative PCR). Tests for human immunodeficiency virus (HIV), cytomegalovirus (CMV) antigen, CMV-RNA, and anti-toxoplasma IgM antibodies were negative. Leflunomide was stopped and the drug elimination was hastened by a two week treatment with cholestyramine.

Within three weeks the neurological status worsened, leading to a progressive motor weakness of the right side, a central paresis of the facial nerve, and a central impairment of bladder function. An MRI follow up disclosed progressive brain lesions. Antiviral treatment was started with 5 mg/kg cidofovir every two weeks. The course of the disease was fluctuating with phases of progression followed by phases of clear improvement of the neurological deficits.

### Patient 2

Four years before admission a 52 year old white man had been diagnosed with WG. After a new onset of haemoptysis, proteinuria, scleritis, and arthralgias, diagnosis was histologically proved by a necrotising, granulomatous vasculitis in a bronchial biopsy specimen and by a positive cANCA (titre 1/100, anti-PR3 positive). With oral cyclophosphamide (2 mg/kg body weight) the clinical course stabilised, except for a residual proteinuria of 0.5 g/day. After 29 months of cyclophosphamide treatment (total dose 95 g), treatment was changed to methotrexate. Two months before admission, a slight increase in arthralgias and fever had developed. Because of suspected WG relapse the treating family doctor increased the daily steroid dose to 50 mg prednisolone a day. The patient was then admitted to our hospital. Because physical examination, a computed tomography scan of the lungs, and laboratory investigations showed no signs of WG activity or of infection, the patient was discharged and tapering of prednisolone was recommended.

Three weeks later he was readmitted because of cough, fever, night sweats, and weight loss of 8 kg. Now, the C reactive protein (CRP) was raised (24 g/l) and the differential blood count showed a lymphocytopenia, with CD4+ T cell counts reduced to  $0.2 \times 10^9/\text{l}$ . An initial chest x ray examination, bronchoscopy, and blood cultures failed to identify any pathogens. Subsequently, the carbon monoxide diffusion capacity was decreased and a new chest x ray examination led to a suspicion of interstitial pneumonia. A bronchoalveolar lavage was performed and showed a chronic inflammation with no signs of pulmonary haemorrhage. All bacterial cultures, PCR for tuberculosis, legionella, and chlamydia, and PCR for Herpes viruses (herpes simplex virus (HSV), CMV, Epstein-Barr virus (EBV)) were negative. Treatment with methotrexate (15 mg weekly) was stopped and a third class cephalosporin and clarithromycin were started. Because the pulmonary function deteriorated, clarithromycin was changed to intravenous co-trimoxazole for suspected *Pneumocystis carinii* pneumonia. Because blood cultures were positive with *Staphylococcus epidermidis*, cephalosporins were replaced by imipenem. With this regimen dyspnoea and CRP levels decreased slightly and improved further when three days later treatment was started with 50 mg of intravenous (IV) prednisolone/day. On the 6th day of this regimen the patient suddenly presented with a generalised seizure. An MRI scan showed numerous small hyperintense lesions disseminated all over the brain (fig 2A) with a homogeneously high signal intensity on diffusion



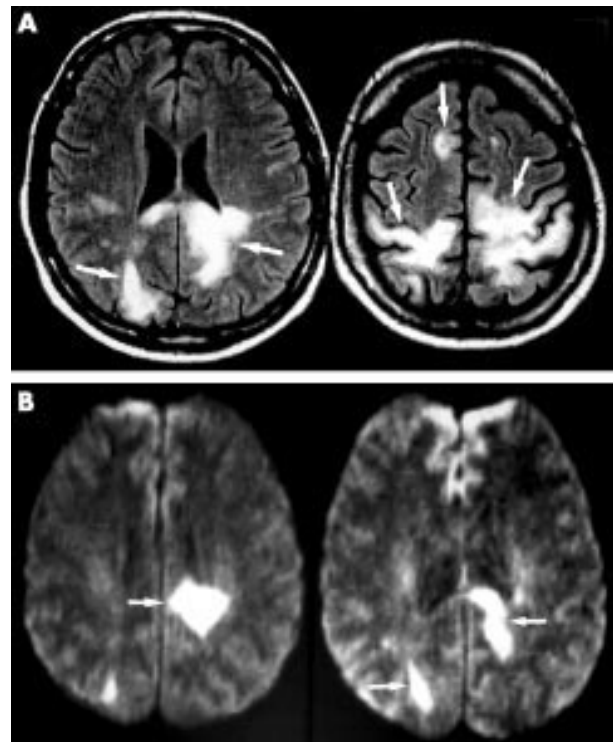
**Figure 2** (A) Numerous ring-enhancing cortical lesions (arrows) with perifocal oedema are demonstrated on the gadolinium-enhanced coronal T<sub>1</sub> weighted MR image. (B) The diffusion weighted axial MR image demonstrates a high signal intensity of the lesions (arrows). Stereotactic brain biopsy showed a pyogenic abscess (patient 2).

weighted images (fig 2B). As serological tests for toxoplasma IgM, aspergillus, borrelia, varicella zoster virus (VZV) IgA, CMV IgM, HSV, HIV were still negative, a stereotactic brain biopsy was performed. Pathological examination showed non-specific inflammation, but microscopic evaluation suggested coryne-like bacteria; the culture confirmed *Nocardia farcinica*. Intravenous co-trimoxazole, the preferred treatment, was continued for 40 days and then switched to oral maintenance treatment. A control MRI scan of the brain showed a complete remission six months later and clinically there was no WG activity detectable despite discontinuation of methotrexate.

Unfortunately, one year later the patient presented with proteinuria (6 g/day) and histological signs of segmental glomerulonephritis. The patient was treated with mycophenolate (1000 mg/day) without recurrence of the nocardia infection during the three month follow up.

### Patient 3

A 55 year old white man complained of difficulties in writing four months before admission. His previous medical history was unremarkable. As the following neurological examinations, including EEG and MRI of the brain, were without clearcut pathological findings, the initial stage of Parkinson's disease was suspected. MRI of the brain was repeated six weeks later and was still normal. One week before admission, fine coordination of the right arm worsened owing to an increased muscle tone and right sided hyperreflexia; the onset of a cerebral palsy was suspected. Now MRI showed multiple hyperintense peri- and paraventricular white matter lesions compatible with vasculitis, multiple sclerosis, or viral infection. HSV, HIV, EBV, CMV, tick-borne encephalitis virus, borreliosis, and lues were serologically excluded. The CSF was



**Figure 3** (A) Axial inversion recovery sequence MRI scan of the brain demonstrates numerous confluent hyperintense lesions in the deep as well as subcortical white matter (arrows) with discrete involvement of the cortex, compatible with vasculitis or viral infection. (B) The diffusion weighted axial MR images demonstrate increased homogeneous diffusion of the brain lesions (arrows) (patient 3).

negative for oligoclonal bands, tick-borne encephalitis virus, and local IgG production. The CSF protein was increased (660 mg/l) while the cell count was normal (1/3 cells). For further evaluation a cerebral angiography was performed and precapillary microaneurysms were detected. Owing to these findings, cerebral vasculitis was suspected and IV pulse steroid therapy was started (1000 mg/day) for five days. When a paresis of the right leg developed, the patient was transferred to our hospital.

On admission an MRI scan of the brain showed multiple confluent non-enhancing lesions of the periventricular, subcortical, and deep white matter with discrete involvement of the cortex (fig 3A). The diffusion weighted MRI scan showed increased diffusion of the brain lesions (fig 3B). Further examinations showed no underlying autoimmune process (negative results for rheumatoid factor, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), antiphospholipid antibodies) or embolic disease. Laboratory findings, including CRP values, were unremarkable with the exception of a steroid induced leucocytosis of  $23.5 \times 10^9/l$  (13% lymphocytes) and a mild hypogammaglobulinaemia (IgG 5.6 g/l, normal range 7–16; IgA 0.6 g/l, normal range 0.7–4). Because of the impression of an accelerated deterioration of the underlying disease cyclophosphamide pulse therapy was started. The patient felt some improvement and was discharged one week later to rehabilitation.

One month later, after the patient had received a second bolus of cyclophosphamide, he became febrile, somnolent, and tetraparetic. On readmission, an MRI scan of the brain showed progressive confluent non-enhancing subcortical white matter lesions. A spinal tap was repeated and the CSF was positive for JC viral DNA. Before treatment could be applied he died with signs of septic shock.

**Table 1** Clinical presentation of primary cerebral involvement of rheumatic diseases and opportunistic CNS infections<sup>6 17 23 24 53 65-67</sup>

Clinical presentation	NPSLE	Primary CNS vasculitis	Wegener's granulomatosis	Neuro-Behçet	Neurosarcoidosis	PML	HSV encephalitis	Bacterial meningitis	Brain abscess
Onset of CNS disease	Acute, subacute, chronic	Acute, subacute, chronic	Subacute, chronic	Acute, subacute, chronic	Acute, subacute, chronic	Subacute (weeks)	Acute, subacute (days-weeks)	Acute (days)	Subacute (days-weeks)
Seizures	13-35%	15-20%	Rare	4%	10%	5%	Frequent	20-30%	20-30%
Headache	34-57%	30-64%	Frequent	95%	30%	5%	Frequent	90%	70-90%
Motor weakness/paresis	20%	50%	?	10-21% Paresis, 24% pyramidal signs	5-10%	33%	Frequent	10-15%	20-50%
Impaired consciousness	5-10%	29%	Rare	Rare	Rare	<1%	Frequent	30-50%	20-30%
Cognitive disorders	12-66%	40-50%	Rare	88%	10%	36%	Frequent	Frequent	?
Psychosis	4-6%	Rare	Rare	2%	Rare	Rare	Rare	Rare	Rare
Mood disorder	10-30%	Rare	Rare	Rare	Rare	Reactive	Rare	Rare	Rare
Visual deficits	5% (vasculitis, neuropathy, amaurosis fugax)	10-15%	Frequent (cranial neuropathy, ocular motor deficits)	1% Optic neuropathy	5-38% Optic neuritis	35% e.g. homonymous hemianopsia	Frequent	Rare	Hemianopsia
Sensory deficits	6-20%	15-20%	?	Up to 27%	5-10%	17%	Rare	Rare	30%
Cerebellar disorders	Rare (infarction)	Rare	Rare	33%	21%	13-32%	Rare	Rare	Ataxia 10%
Cranial nerve involvement	5-35%	Frequent	Frequent	25% Ophthalmoplegia, 10-15% bulbar paresis	50-72% Cranial nerve palsies	Rare	Rare	10 (N. III, VI, VII, VIII)	Rare
CRP	Normal	Normal	Frequently ↑	Frequently ↑	Normal ↑	Normal ↑	normal - ↑	↑	↑
Other	<1% Transverse myelitis, 2-5% chorea	30% Aphasia	Chronic meningitis, myelopathy	8% Meningo-encephalitis, 6% movement disorders	5-12% Meningitis, 10-28% myelitis, 10% hypothalamic and pituitary dysfunction	Impaired speech	Wernicke aphasia, dysphasia	Meningism, fever, erythema	50% Fever, 25-30% meningism

NPSLE, neuropsychiatric systemic lupus erythematosus; PML, progressive multifocal leucoencephalopathy; HSV, herpes simplex virus; ?, no data from clinical trials available.

**Table 2** MRI findings in primary cerebral involvement of rheumatic diseases and opportunistic CNS infection<sup>8 15 18 21 23 52 53 66-68</sup>

MRI findings	NPSLE	Primary CNS vasculitis	Wegener's granulomatosis	Neuro-Behçet	Neurosarcoidosis	PML	HSV encephalitis	Bacterial meningitis	Brain abscess
Normal	13-50%	0-50%	50%	30%	11%	Only in the early phase	Rare	?	Rare
Territorial infarction	15-30%	Frequently (e.g. middle cerebral artery)	15-20%	18%	Rare	-	-	-	-
In T <sub>2</sub> hyperintense lesions of the cortex	0-9% Reversible	Rare	Cerebral granulomas (homogeneous, ring enhancement)	36-66% Mes-, diencephalic, 26% isolated brain stem or basal ganglia	30% Multiple or solitary supra- and/or infratentorial, rarely brain stem or cerebellum	56% Thalamus, 32% posterior fossa	Haemorrh. necrosis temporal, insula, thalamus, hippoc., subfrontal	-	Frequent
White matter lesions (WML)	30-75% Subcortical > deep white matter > periventricular	Frequent infarcts often in the deep white matter	50% Periventricular, subcortical	16% Para- and periventricular	40% Peri- and paraventricular, subcortical, confluent	100% Subcortical, 93% parieto-occipital, 92% bilateral, 94% confluent, no mass effect	-	-	Frequent, capsule with low intensity signal, indistinct margins between abscess and surrounding
GDTPA enhancement of WML or cortical lesions	Only active lesions	Active lesions	Active lesions	Often but only active lesions	Often nodular or annular enhancement	<10% Enhancement of the periphery	Often	-	Strong contrast enhancement
Atrophy	10-60%	Chronic stage	42%	20% Brain stem	?	69%	-	-	-
Other		Rarely meningeal enhancement	2-30% Focal or diffuse meningeal/dural thickening	spinal cord lesions	38-57% Nodular or diffuse meningeal enhancement, 28% optic nerve enhancement	58% Infratentorial (e.g. brain stem), no perifocal oedema	Often brain oedema associated with the lesions	Meningeal enhance., nodular lesions	Mass effect

GDTPA, gadolinium-DTPA.



**Table 3** Cerebrospinal fluid (CSF) findings in primary cerebral involvement of rheumatic diseases and opportunistic CNS infections<sup>9 10 17 19 22 23 53 56 57 66-72</sup>

CSF findings	NPSLE	Primary CNS vasculitis	Wegener's granulomatosis	Neuro-Behçet	Neurosarcoidosis	PML	HSV encephalitis	Bacterial meningitis	Brain abscess
Normal findings	50%	10-90%	?	25-30%	19%	70%	Only in early stages	-	20%
Pleocytosis	27-32%	20-50%	?	50-60%	50-70%	20%		100%	80%
Cell count	20-100	10-150	10-100	0-1100 (mean 80)	5-200	?	2-200	>1000	0-1000
Cell type	Lymphocytes	Lymphocytes	Lymphocytes	Lymphocytes ± granulocytes	Lymphocytes	?	Lymphocytes, initially granulocytes	Granulocytes	Granulocytes
Raised protein content (mg/l)	30-48%	30%	?	60%	73%	30%	500-2000	>1000	>1000
IgG index >0.6	500-1000	190-2300	500-1000	500-2000	500-1000	?	90%	?	?
Oligoclonal bands	30%	Rare	?	73%	18.5%	?	-	-	-
Other	25-42% Reversibility	Rare	?	16-20% Reversibility	4% CSF glucose <50% of serum glucose, 33-50% CSF ACE raised	Rare	HSV-DNA-PCR Sensitivity 95%, Specificity 95%	Gram staining positive, CSF glucose <50%, CSF lactate >3.5 mmol/l	Gram staining negative

ACE, angiotensin converting enzyme; CSF, cerebrospinal fluid; IgG index, CSF IgG/serum IgG (normal value &lt;0.6); protein content (normal value 180-430 mg/l); JCV, JC virus.

## DISCUSSION

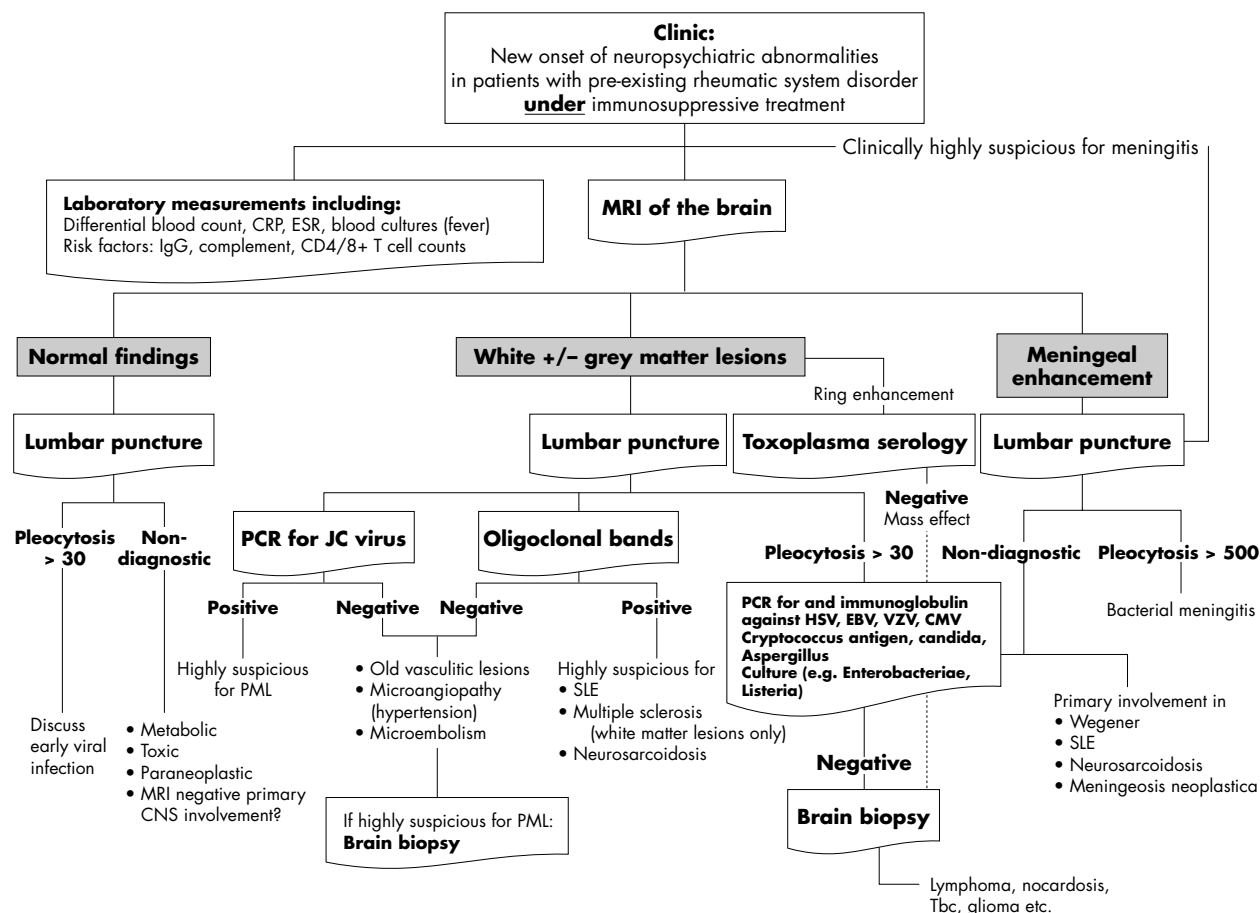
In recent years morbidity and mortality of autoimmune diseases—partly due to effective immunosuppressive treatment—are increasingly related to secondary infections.<sup>25 26</sup> Cerebral involvement, especially, makes differential diagnosis difficult. Often the clinical presentation does not allow discernment between primary angiitis of the CNS, secondary CNS involvement of rheumatic diseases, and CNS infection, because the signs and symptoms are non-specific (table 1). Also, MR images (table 2) and laboratory findings, including CSF analysis (table 3), are rarely specific. Only a combination of several diagnostic procedures, additional specific serological tests, and, if possible, stereotactic brain biopsy permit a firm diagnosis.

Here we review the current literature on PML and nocardiosis in systemic rheumatic disease and present a diagnostic algorithm for immunosuppressed patients with new onset or worsening of neuropsychiatric symptoms.

In the past 10 years JC virus has been recognised as an important pathogen in patients receiving immunosuppressive treatment.<sup>27</sup> It is mainly associated with advanced HIV infection and causes PML, a fatal demyelinating JC virus induced disorder of the CNS.<sup>28</sup> Reports on at least 20 cases of patients with PML receiving corticosteroids and cytotoxic drugs for rheumatic disease have been published: 11 patients with SLE,<sup>29-38</sup> three patients with rheumatoid arthritis,<sup>39-41</sup> three patients with WG,<sup>42-44</sup> two patients with inflammatory myositis,<sup>45 46</sup> and one patient with mixed connective tissue disease.<sup>47</sup>

Among healthy volunteers, 65-90% have antibodies against, and are carriers of, the JC virus. One study demonstrated a correlation between JC viruria and treatment with corticosteroids and cytotoxic drugs,<sup>27</sup> whereas others found no relationship.<sup>48</sup> The development of PML does not seem to depend on distinct immunosuppressant drugs: corticosteroids, cyclophosphamide, chlorambucil, azathioprine, cyclosporin A, and leflunomide (patient No 1) have all been associated with the occurrence of PML in case reports. Low CD4+ T cell counts may predispose for opportunistic CNS infections such as cerebral toxoplasmosis. However, CD4+ T cell depletion alone is not sufficient to define a high risk of PML. Indeed, experience with HIV infection showed that 11% of patients with a clinical manifestation of PML have a CD4+ cell count above  $0.2 \times 10^9/l$ ,<sup>28 49</sup> an observation which is in accordance with the normal CD4+ T cell count in our patient No 1. A relatively high CD4+ T cell count at the onset of PML suggests either a loss of JC virus-specific memory CD4+ T cells or other risk factors leading to viral replication in the brain. Interestingly, hypogammaglobulinaemia was associated in one reported case<sup>50</sup> as well as in our patient No 3. In some patients with SLE, complement deficiency may contribute to the immune defect, with a particular risk of developing serious infections with encapsulated organisms such as *Streptococcus pneumoniae* and *Neisseria meningitidis*.<sup>51</sup> Unclear is the role of the phagocytic system and local factors in the control of PML induced by JC virus.

Table 1 summarises the clinical manifestations of PML. Abnormalities of the motor function are most common. Fever, headache, neck stiffness, or impaired consciousness are rare. PML lesions begin as small foci in the white matter and expand concentrically, either at one or several sites. In later stages of the disease MR images are strongly suggestive of the diagnosis. Typically, PML appears as bilateral, asymmetrically distributed, confluent (>90%), predominantly subcortical white matter lesions which develop close to the grey-white matter junction and in the periventricular region. They show high signal intensity on T<sub>2</sub> weighted imaging and low signal intensity in T<sub>1</sub> weighted series. The grey matter, especially the thalamus, can be affected in up to 50% of patients (table 2).<sup>52</sup> Usually, lesions of PML are not enhanced by gadolinium-DTPA. Rarely, a faint peripheral enhancement is seen,<sup>53</sup> which



**Figure 4** Diagnostic approach to brain diseases in immunosuppressed patients with pre-existing rheumatic diseases. The measurement of IgG, complement level, and CD4/8+ T cell count is not evidence based.

is interpreted as an indicator of an immune response to viral antigens in long term survivors.<sup>54</sup> Despite a rather characteristic presentation of advanced PML in MRI analysis the differential diagnosis remains a challenge, because cases of central nervous system SLE mimicking PML have been reported.<sup>55</sup> Therefore, the next step in confirming a suspected diagnosis of PML must be analysis of the CSF for the presence of JC virus DNA by PCR.<sup>56–57</sup> This test reaches a sensitivity of 93% and a specificity of 99% while PCR analysis performed in urine or blood samples was not specific for PML.<sup>56</sup> Whether the viral load correlates with the prognosis is still being debated. The firm diagnosis—unfortunately often post mortem—is made by histological examination, showing enlarged oligodendrocytes with an expanded cytoplasmic compartment and intranuclear inclusions (“ground glass”), which represent the polyoma viruses. Therefore, stereotactic brain biopsy is strongly recommended in all cases of suspected PML and negative JC virus PCR in CSF samples.

The primary differential diagnoses include other viral infections (HIV, HSV, CMV), toxoplasmosis, neuropsychiatric SLE (in patients with known SLE), lymphoma, toxic encephalitis after chemotherapy, vasculitis, and neurosarcoidosis (tables 2 and 3). Interestingly, the vascular lesions shown by cerebral angiography in patient No 3 strongly argue against PML as the cause of the primary symptoms in this patient. On the other hand, it has to be kept in mind, that several infectious agents have to be ruled out in the assessment of patients with possible cerebral vasculitis, because a variety of pathogens have a propensity to affect blood vessels—for example, aspergillus, candidiasis, cysticercosis, coccidioidomycosis, *Strongyloides stercoralis*, arbovirus, VZV, and hepatitis C virus infection.<sup>58–59</sup>

The prognosis for PML is usually poor. No effective treatment is available at present; anecdotal reports show some efficacy of cidofovir, interferon alfa, and cytosine arabinoside.<sup>60</sup> Nevertheless, PML may remit if the underlying immunodeficiency improves,<sup>54</sup> therefore discontinuation of immunosuppressive agents should receive a high priority.<sup>60</sup>

MRI findings of early white matter lesions caused by JC virus are non-specific and may be indistinguishable from early brain abscesses. However, contrast enhancement or mass effects of the lesions visualised by MRI helps to distinguish cerebral abscesses from PML and HSV encephalitis. Differential diagnosis includes primary brain tumours, metastasis, or cerebrovascular events.

Symptoms in patients with brain abscess are headache, fever, focal neurological deficits, confusion, meningitis and seizures, all of which may also occur in patients with cerebral metastasis or CNS involvement due to ANA or ANCA positive vasculitis. However, fever and meningitis are rarely seen in systemic rheumatic diseases, with the exception of WG.<sup>61</sup> If a spinal tap is contraindicated owing to the mass effect of the brain abscess, the preferred diagnostic procedures are stereotactic brain biopsy followed by histological and microbiological analysis.

Typical microbes which can cause brain abscess formation are *Toxoplasma gondii*, fungi (aspergillus, candida, or cryptococci), mycobacteriosis, *Listeria monocytogenes*, and *Nocardia asteroides*. Thirty two cases of SLE associated nocardiosis have been reported.<sup>62</sup> Lungs, skin, and brain were the organs most commonly affected. Nocardiosis of the CNS was found in up to 30% of these patients and was associated with a high mortality.<sup>62</sup> Nocardia should be kept in mind as a possible pathogen in patients whose infections do not respond to third

generation cephalosporins.<sup>63</sup> Preferred antibiotics are trimethoprim-sulfamethoxazole and imipenem.

We reviewed the current literature to assess whether there exist specific signs to differentiate between CNS involvement of systemic rheumatic diseases and CNS infection. As shown in tables 1–3, the clinical distinction is always vague and remains difficult in certain patients because of overlapping clinical features. Differential diagnosis includes toxic leukoencephalopathy caused by therapeutic agents (for example, cyclosporin, tacrolimus, amphotericin B, antineoplastic therapeutic drugs),<sup>64</sup> hypertensive encephalopathy, and metabolic complication involving the nervous system, such as hydroelectrolytic changes.

Finally, what are the lessons taught from our three cases? Firstly, in patients who are strongly immunosuppressed, the new onset or change of cerebral symptoms should alert the doctor to look carefully for opportunistic infections. Blood cultures and brain imaging (MRI) should be the first step of the clinical evaluation (fig 4). If CNS infection, especially bacterial meningitis or abscess formation, cannot be ruled out, empirical treatment should be started following the guidelines for immunosuppressed patients. In patients with mass effect of brain lesions, stereotactic brain biopsy should be started without delay, otherwise spinal tap and CSF analysis including PCR to detect JC virus, HSV, VZV, EBV, and CMV should be performed. The diagnosis of nervous system infection may also be confirmed by the presence of antibodies to HSV, VZV, EBV or CMV in the CSF even without detectable DNA.<sup>73</sup>

Secondly, in cases where the diagnosis is not clear we suggest that immunosuppression should not be intensified until an opportunistic infection has clearly been ruled out. An alternative strategy in this setting would be the treatment with intravenous immunoglobulins (IV IgG) combined with antibiotics, especially in patients who have hypogammaglobulinaemia. In several autoimmune diseases—for example, SLE and ANCA positive vasculitis, uncontrolled studies have suggested that IV IgG may be an effective therapeutic option.<sup>74</sup> IV IgG treatment has also been shown to decrease the frequency and severity of exacerbations in multiple sclerosis.<sup>75</sup> Polyvalent immunoglobulins have complex immunoregulatory effects, including the neutralisation of microbial toxins, and contain a broad range of antibodies against pathogens.<sup>74</sup> Because the efficacy of IV IgG is not documented in CNS manifestations of systemic rheumatic diseases, this treatment strategy should be restricted to patients with hypogammaglobulinaemia until controlled trials demonstrate a clear benefit.

Because CNS infection carries a high mortality rate and full recovery can be expected only in a small percentage of patients, multicentre studies are warranted to answer the following questions: (a) Which factors define patients at risk for opportunistic CNS infections in systemic rheumatic diseases? (b) Which imaging procedure may help to detect and distinguish CNS infection in these patients?

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